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REVIEW ARTICLE

Azilsartan and Chlorthalidone-New Powerful Fixed dose Antihypertensive Combination

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Abstract: Arterial hypertension is a disease that still affects a major part of the population worldwide, and leads to fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions. From the CDC statistical analysis, as regarding to United States, 1 of every 3 adults has high blood pressure, and only about half (54%) of them have it under control. Furthermore, all that leads to a nation cost about $46 billion each year. Efforts to find new ways to regulate arterial hypertension are therefore imperative.

In our days, a lot of references have been made to the use of a new therapeutic combination, that of azilsartan – an innovative ARB, in combination with chlorthalidone. In fact, it is a combination now prescribed in a number of countries.

A significant number of trials shows both azilsartan vs popular antihypertensive drugs, as well as chlorthalidone vs chlorothiazide, to present a better antihypertensive effect. This effect is even greater when the two substances are combined. In this article, we will try to present the latest findings concerning the efficacy, safety and clinical utility of this combination, as well as its adverse events, in comparison with other widely used therapeutic options.

Keywords: Azilsartan medoxomil, chlorthalidone, combination, hypertension.

INTRODUCTION

Hypertension remains one of the biggest and poorly controlled health problems even in our days, leading to coronary heart disease, stroke, heart failure, and kidney disease. New antihypertensive agents continue to be developed in the effort to combat the problem of hypertension. According to ACC/AHA hypertension guidelines, antihypertensive therapy is recommended for: I) patients with clinical cardiovascular disease and systolic blood pressure (SBP) ≥130 mm Hg or a diastolic blood pressure (DBP) ≥80 mm Hg, II) adults without cardiovascular disease but with an estimated 10-year atherosclerotic cardiovascular disease risk of ≥10% and SBP ≥130 mm Hg or DBP ≥80 mm Hg, III) adults without cardiovascular disease and with an estimated 10-year atherosclerotic cardiovascular disease risk <10% and a SBP ≥140 mm Hg or a DBP ≥90 mm Hg [1].

The combination therapy of azilsartan and chlorthalidone is a promising new approach for the treatment of hypertension with positive results from several trials, approved on December 20, 2011 by the US Food and Drug Administration (FDA). Azilsartan is a new angiotensin receptor blocker (ARB) with a unique structure that provides her with increased antihypertensive effectiveness, while chlorthalidone on the other hand was commonly used in the 1970s, but in our days it is not a popular treatment, without any specific cause from what is known. In this article we will list the newest studies that compare each of them separately but also their combination with other more traditional therapies. Pubmed was used as our database. The keywords of our search strategy were "azilsartan", "azilsartan-medoxomil", "anihypertensive therapy", "antihypertensive result", "antihypertensive effect", "blood pressure". Articles published in English were included only. Additional relevant studies were included by manual search, using references from other review articles and clinical trials.

AZILSARTAN MEDOXOMIL

Azilsartan Medoxomil(AZL-M) is the newest used ARB for the therapy of hypertension. It is a prodrug that is further hydrolyzed to the active moiety azilsartan in the gastrointestinal tract. It is estimated to have a bioavailability of 58%, a peak plasma concentration at 1.5 to 3 hours and a half life at 11 hours. Its metabolism occurs mainly through the cytochrome P450 (CYP) 2C9 and less on CYP2B6 and CYP2C8. Its inactive metabolites are mainly excreted by the kidneys.

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The renal clearance of azilsartan is 2.3 mL/minute. Steady state plasma concentrations after oral administration are measured by day five [2].

COMPARISON OF AZILSARTAN WITH OTHER ARBS AND RAMIPRIL

Clinical trials that compared AZL-M vs placebo or active therapy (olmesartan, valsartan, candesartan or ramipril) and an observational registry comparing AZL-M with ACE inhibitors, have shown superiority of AZL-M at improving the trials' primary end point of clinic or ambulatory systolic blood pressure. Adverse effects were reported to be similar in all treatment groups, mild to moderate in severity mostly, such as dizziness, headaches, urinary infections and upper respiratory tract inflammation. The clinical trials that were found according to our search criteria are listed below.

Bakris *et al.* studied the antihypertensive efficacy and safety of AZL-M, olmesartan medoxomil (OLM-M) and placebo in a randomized, double-blind, placebo controlled, multicenter study. A number of 1275 patients with primary hypertension and baseline 24-hour mean ambulatory SBP between ≥130 mm Hg and ≤170 mm Hg participated, following 6 weeks of treatment. 142 received placebo and the remaining participants received 20 mg, 40 mg, or 80 mg AZL-M or 40 mg OLM-M. The study showed that the reduction in 24-hour mean SBP was greater with AZL-M 80 mg than OLM-M 40 mg (80 mg, -14.6 mmHg; 40 mg, -12.6 mmHg. P= 0.038) while AZL-M 40 mg(-13.5 mmHg) was noninferior to OLM-M 40 mg. The side effect profiles of both ARBs were similar to placebo [3].

White *et al.* compared the antihypertensive efficacy and safety of AZL-M, OLM-M, valsartan(VAL) and placebo in a randomized, double-blind, placebo-controlled trial using ambulatory blood pressure (BP) monitoring and clinic BP measurements. 1291 patients with clinic SBP between ≥150 mm Hg and ≤180 mm Hg and 24-hour mean SBP between ≥130 mm Hg and ≤170 mm Hg participated. The patients were randomly assigned to placebo, 20 or 40 mg of AZL-M, 160 mg of VAL, or 20 mg of OLM-M once daily for 2 weeks, and then were force-titrated to 40 or 80 mg of AZL-M, 320 mg of VAL, 40 mg of OLM-M, or continuation of placebo once daily for an additional 4 weeks. The study showed that AZL-M at 80 mg had superior efficacy to both VAL at 320 mg and OLM-M at 40 mg: placebo-adjusted 24-hour SBP was lowered (−14.3 mm Hg) more than 320 mg of VAL (−10.0 mm Hg; P<0.001) and 40 mg of OLM-M (−11.7 mm Hg; P=0.009). AZL-M at 40 mg was noninferior to 40 mg of OLM-M (difference: −1.4 mm Hg). Safety and tolerability were similar among the placebo and 4 active treatments [4].

Sica *et al.* compared the effects of AZL-M and VAL in a randomized, double-blind, multicenter study using ambulatory and clinic BP measurements. 984 patients were included if their clinic SBP was ≥150 mm Hg and ≤180 mm Hg and 24-hour mean SBP was ≥130 mm Hg and ≤170 mm Hg. They were assigned into 3 groups: AZL-M 20 mg every day force-titrated to 40 mg every day after 2 weeks, AZL-M 20 mg every day force-titrated to 80 mg every day after 2 weeks, or VAL 80 mg every day force-titrated to 320 mg every day after 2 weeks, with continued treatment for an additional 22 weeks. This trial showed AZL-M 40 mg and 80 mg lowered 24-hour mean SBP (−14.9 mm Hg and −15.3 mm Hg, respectively) more than VAL 320 mg (−11.3 mm Hg; p< 0.001 for 40-mg and 80-mg comparisons vs VAL). Small, reversible changes in serum creatinine occurred more often with AZL-M than with VAL. Besides that, safety and tolerability parameters were similar among the three groups [5].

Rakugi *et al.* compared the efficacy and safety of AZL-M (20–40 mg once daily by forced titration) with that of candesartan cilexetil(CAND) for 24-h blood pressure control in a multicenter randomized, double-blind study. 622 Japanese patients with a sitting DBP of ⩾95 and <110 mm Hg, and a sitting SBP of ⩾150 and <180 mm Hg, followed a 16 weeks treatment. After a 4-week placebo run-in period, eligible patients were randomized equally to receive either AZL-M (dosage of 20 mg daily for the first 8 weeks and then 40 mg daily for the subsequent 8 weeks) or candesartan (dosage of 8 mg daily for the first 8 weeks and then 12 mg daily for the subsequent 8 weeks). This study showed that the mean change from baseline in sitting DBP at week 16 (primary endpoint) was −12.4 mm Hg in the AZL-M group and −9.8 mm Hg in the CAND group (difference: −2.6 mm Hg, P=0.0003). Safety and tolerability were similar among the two groups [6].

Bonner *et al.* compared the antihypertensive efficacy and safety of AZL-M vs the ACE inhibitor ramipril (RAM) in patients with clinic SBP 150–180 mm Hg in a double-blind, controlled, randomized trial. 884 patients were randomised to 20 mg AZL-M or 2.5 mg RAM for 2 weeks, then force-titrated to 40 or 80 mg AZL-M or 10 mg RAM for 22 weeks. Clinic SBP decreased by 20.6±0.95 mm Hg and 21.2±0.95 mm Hg with AZL-M 40 and 80 mg vs 12.2±0.95 mm Hg with RAM (P<0.001 for both AZL-M doses). Adverse events were less frequent with AZL-M 40 and 80 mg than with RAM [7].

The EARLY Gitt *et al.* registry is a prospective, observational, national, multicentre registry with a follow-up period of 12 months. There were two principal objectives: the documentation of the achievement of target BP values set according to recent guidelines and the description of the safety profile of AZL-M. A total of 3849 patients who initiated monotherapy at baseline comprising either AZL-M or an ACE-inhibitor were included at a ratio of seven to three. Results showed that a BP target of <140/90 mmHg was achieved by a significantly greater proportion of patients in the AZL-M group (61.1 %) compared with the ACE-inhibitor group (56.4 %; p < 0.05), with safety similar to both groups [8].

This superiority of AZL-M may be explained by another study that shows AZL-M to bind tightly and dissociate slowly from AT_1 receptors compared with other ARBs. This behavior, may be attributable to its chemical structure. AZL-M, like OLM-M and CAND, has a carboxyl group that is suggested to interact with the amino acid lysine and provide tight binding to AT1. In addition to the carboxyl group, AZL-M also has an oxadiazolone group in place of the tetrazole ring, in contrast with the other ARBs. This structure

Table 1. Clinical trials comparing azilsartan vs placebo or active therapy.

Study	Type of Study	Number of Patients	Duration	Treatment	Primary end-Point	Result
Bakris *et al.*	RCT double blind	1275	6 weeks	AZL-M (20,40,80 mg) or OLM (40 mg) or placebo	Reduction in 24-hour mean SBP	AZL-M 80 mg (−14.6mmHg) vs. OLM 40 mg (−12.6 mmHg) (p = 0.038) AZL-M 40 mg (−13.4 mmHg) vs OLM 40 mg non inferior
White *et al.*	RCT double blind	1291	6 weeks	AZL-M (40,80 mg) or VAL (320 mg) or OLM (40 mg) or placebo	Reduction in 24-hour mean SBP	AZL-M 80 mg (−14.3 mmHg) vs. OLM 40 mg (–11.7 mmHg) (p = 0.009) and VAL 320 mg (−10.0 mmHg) (p < 0.001) AZL-M 40 mg vs OLM 40 mg non inferior (difference: −1.4 mm Hg)
Sica *et al.*	RCT double blind	984	24 weeks	AZL-M (40,80 mg) or VAL (320 mg)	Reduction in 24-hour mean SBP	AZL-M 40 mg (−14.9 mmHg) and 80 mg (−15.3 mmHg) vs. VAL (−11.3 mmHg) (p < 0.001 for both)
Rakugi *et al.*	RCT double blind	622	16 weeks	AZL-M (20–40 mg) or CAND (8–12 mg)	Reduction in mean sitting DBP	AZL-M 20-40 mg (−12.4 mmHg) vs. CAND 8-12 mg (−9.8 mmHg) (p = 0.0003)
Bonner *et al.*	RCT double blind	884	24 weeks	AZL-M (20-40 or 20–80 mg) or RAM (2.5–10 mg)	Reduction in clinic SBP	AZL-M 40 mg (−20.6±0.95 mmHg) and AZL-M 80 mg (−21.2±0.95 mm Hg) vs. RAM (–12.2±0.95 mm Hg) (p < 0.001)
EARLY Gitt *et al.*	Prospective, observational registry	3849	12 months	AZL-M or ACE-inhibitor	I)Documentation of the achievement of target BP values set according to recent guidelines II)Description of the safety profile of AZL-M	Target BP (<140/90 mmHg) achieved in AZL-M group (61.1% of patients) vs. ACE- inhibitors group (56.4% of patients) (p < 0.05) Similar safety profile

RCT, randomized controlled trial; AZL-M, Azilsartan Medoxomil; OLM, olmesartan; RAM, ramipril; VAL, valsartan; CAND, candesartan; ACE, angiotensin converting enzyme; SBP, systolic blood pressure; DBP, diastolic blood pressure; BP, blood pressure.

could explain further the strongest binding and antihypertensive action of AZL-M [9].

CHLORTHALIDONE

Chlorthalidone is a thiazide-like diuretic that differs structurally from hydrochlorothiazide, with it's diuretic effect produced at the cortical diluting segment of the ascending loop of Henle, resulting in expanding urine volume and in decreasing extracellular fluid volume, plasma volume and exchangeable sodium. Natriuretic effect begins approximately 2.6 hours after drug administration and can be sustained for 48-72 hours [10].

COMPARISON OF CHLORTHALIDONE WITH HYDROCHLOROTHIAZIDE

Hydrochlorothiazide and chlorthalidone have been the two most commonly used diuretics, with hydrochlorothiazide still been the most commonly prescripted. However, the scientific community is increasingly thinking of chlorthalidone as superior with greater antihypertensive action and association with fewer cardiovascular events.

First to show superiority of chlorthalidone was a randomized primary prevention trial (MRFIT) that tested the effect of a multifactor intervention program on coronary heart disease. Participants were randomly assigned to either a special intervention program (SI) (dietary advice for lowering blood cholesterol levels, counseling aimed at cessation for cigarette smokers, and stepped-care treatment for hypertension) or to their usual sources of health care within the community (UC). The favorable posttrial mortality findings for the SI group seem to be also related to a replacement in the diuretic treatment of hydrochlorothiazide(HCTZ) with chlorthalidone(CLD) at a daily maximum dose of 50 mg, due to a +44.1% higher coronary heart disease mortality in clinics predominantly prescribing HCTZ compared to the usual care group (P = 0.23), while on the other hand the clinics predominantly prescribing CLD had a −58.2% lower coronary heart disease mortality compared to usual care. After the replacement, mortality in the previously predominant HCTZ prescribing clinics decreased to −7.9% [11].

The retrospective observational cohort analysis of the Multiple Risk Factor Intervention Trial by Dorsch *et al.* fur-

ther studied the superiority of CLD vs HCTZ suggested by the MRFIT and shown that cardiovascular events were 21% lower with CLD vs HCTZ after a median follow-up period of 6 years ($p = 0.0016$). Furthermore, the CLD group had significantly lower BP ($p < 0.0001$), total cholesterol ($p < 0.0001$), and low-density lipoprotein cholesterol ($p = 0.0009$) levels compared with the HCTZ group, but it was also related to higher serum uric acid and lower potassium levels [12].

Similarly, a network meta-analysis of nine randomized trials in which one arm was either CLD or HCTZ, indicated that CLD was better than HCTZ for preventing cardiovascular events in patients with hypertension, with a reduction of 21% ($P<0.0001$), relative to HCTZ [13]. In contrast to the previous results, a propensity score–matched observational cohort study with up to 5 years of follow-up of 29 873 patients, who were newly treated with CLD or HCTZ and were not hospitalized for heart failure, stroke or myocardial infarction in the prior year, did not show association of CLD with fewer adverse cardiovascular events or deaths than HCTZ, but nonetheless, it was associated with a greater incidence of electrolyte disorders, mainly hypokalemia [14].

Another small randomized, single-blinded, crossover study compared CLD 12.5 mg/day (force-titrated to 25 mg/day) and HCTZ 25 mg/day (force-titrated to 50 mg/day) in untreated hypertensive patients, in a 8-week active treatment, and revealed a greater reduction from baseline in SBP with CLD 25 mg/day compared with HCTZ 50 mg/day, with statistical significance at nighttime ambulatory SBP (24-hour mean = −12.4 mm Hg versus −7.4 mm Hg; $P=0.054$; nighttime mean = −13.5 mm Hg versus −6.4 mmHg; $P=0.009$). However reductions were statistically similar by week 8, as regarding office BP. Changes in serum potassium were similar between the two groups [15].

In a meta-analysis that included randomized, double-blind, parallel placebo-controlled trials (following criteria: ≥2 different monotherapy dose arms, follow-up duration ≥4 weeks, baseline washout of medication ≥2 weeks) and studied the dose-response of HCTZ, CLD, and bendroflumethiazide on BP, serum potassium and urate, revealed a potency series: bendroflumethiazide>CLD>HCTZ (the estimated dose predicted to reduce systolic BP by 10 mm Hg was 1.4, 8.6, and 26.4 mg, respectively). Potency series for DBP was similar to that seen for SBP [16].

Additionally, a double-blind, double-dummy, randomized, parallel group, comparative, multicentric trial, studied Indian patients, between 18 and 65 years of age with stage 1 essential hypertension (office SBP between 140 and 159 mm Hg and DBP between 90 and 99 mm Hg), who were randomized to receive treatment with a once-daily dose of CLD 6.25 mg, or HCTZ - controlled released 12.5 mg or conventional HCTZ 12.5-mg tablets for 12 weeks, after a 2-week placebo treated- wash out period. The results showed that the 24-h ambulatory SBP was significantly lower in the CLD group than in the HCTZ group at weeks 4 ($p = 0.019$) and 12 ($p = 0.013$), concluding that HCTZ, at the dose of 12.5 mg daily failed to significantly lower 24-h ambulatory BP after 12 weeks of monotherapy, therefore cannot be used as monotherapy in contrast with CLD [17].

Another retrospective analysis, with data extracted from a large health plan from January 1/2005 to December 31/2012 of patients who were initially prescribed CLD or HCTZ, showed higher percentage on achieving goal SBP/DBP values with CLD (45.0%/78.3%) than with either HCTZ 25 mg (32.1%/63.9%) or HCTZ 50 mg (32.8%/68.9%) ($p< 0.05$ for all), without clinically significant differences in serum potassium [18].

The superiority of CLD that is suggested by multiple studies could be asssociated with its pharmacokinetics and pharmacodynamics characteristics. In a literature search that included studies from 1960 to 2003 that evaluated the pharmacokinetic and blood pressure–lowering effects of CLD and HCTZ, turned out CLD to be approximately 1.5 to 2.0 times as potent as HCTZ at equivalent doses. Furthermore CLD has a longer duration of action than does HCTZ. (24-72 hours vs 12-24 hours). It's prolonged terminal half life in comparison with HCTZ, could be explained by it's rapid concentration and slow release from the erythrocytes [19].

AZILSARTAN-CHLORTHALIDONE COMBINATION THERAPY

It is well known that most patients need more than a antihypertensive drug to control blood pressure. The combination of drugs seems to provide better results than doubling the dose of the initial drug due to both the synergistic action and the reduction of the risk of side effects. Polypharmacy, on the other hand, is associated with low patient compliance. A fixed-dose combination seems to be a solution, simplify-

Table 2. Differences of Chlorthalidone vs Hydrochlorothiazide pharmacokinetics, pharmacodynamics, estimated potency and adverse effects (12,16,18).

	Chlorthalidone	Hydrochlorothiazide
Type	thiazide-like diuretic	benzothiadiazine
Peak concentrations	2 -6 hours	2 hours
Half life	45 to 60 hours	8 -15 hours
Potency (approximal estimation)	1.5 – 2 time as potent as Hydrochlorothiazide	
Hypokaliemia , hyperuricemia	More likely with Chlorthalidone	

ing an antihypertensive dose regimen. A fixed dose combination therapy with a renin-angiotensin system (RAS) inhibitor (an ACE inhibitor or an ARB) plus a diuretic is a widespread and effective treatment [20-25].

Sica *et al.* compared in a double-blind factorial, the efficacy and safety of fixed-dose combinations of AZL-M and CLD with the individual monotherapies. 1714 patients with clinic SBP: 160 mm Hg to 190 mm Hg were randomized to AZL-M 0 mg, 20 mg, 40 mg, or 80 mg and/or CLD 0 mg, 12.5 mg, or 25 mg for an 8-week treatment. For the fixed dose, combinations of AZL-M/CLD 40/25-mg and 80/25-mg, SBP reduction was 28.9 mm Hg and exceeded AZL-M 80 mg and CLD 25 mg monotherapies by 13.8 mm Hg and 13 mm Hg, respectively ($p< 0.001$ for both comparisons). Elevation of serum creatinine levels was dose-dependent and occurred more often in the AZL-M/CLD groups [26].

Cushman *et al.* compared the fixed dose combinations of AZL-M/CLD force titrated to a high dose of either 40/25 mg or 80/25 mg with OLM-M/HCTZ force titrated to 40/25 mg in a double-blind randomized controlled trial, over a 12 week treatment period. 1071 participants with baseline SBP between 160 to 190 mmHg and DBP <119 mmHg were randomized. Changes in SBP at week 12 were significantly greater in both AZL-M/CLD arms than in the OLM-M/HCTZ arm (42.5 mmHg, 44.5 mmHg and 37.1 mmHg respectively, $p< 0.001$ for all comparisons). However, the approximate equivalent dose of CLD 25 mg is HCTZ 50 mg, so it is possible that the doses compared were unequal [27].

Bakris *et al.* compared the fixed dose combinations of AZL-M/ CLD and AZL-M/HCTZ in a double-blind randomized controlled trial, following a 10 weeks treatment. 609 patients with stage 2 primary hypertension first received AZL-M 40 mg for 2 weeks and then were randomized to receive 12.5 mg of CLD or HCTZ in addition to AZL-M for 4 weeks, titrated up to 25 mg for 4 more weeks if BP was not controlled. AZL/CLD combinations provided greater reduction in SBP than AZL/HCTZ combinations (35.1 mmHg versus 29.5 mmHg, $p< 0.001$), with a greater percentage of achieving target BP at week 6 (64.1% versus 45.9%, $p< 0.001$) (paragraph 4, line 11). Discontinuation of the treatment due to adverse events was not statistically significant between both groups (9.3% versus 7.3%, $P = 0.38$), and hypokalemia was uncommon in both groups. Similar to the study of Cushman *et al.*, it is possible that the doses compared were unequal [28].

It is well known that hypertension, metabolic syndrome (MetS) and chronic kidney disease are linked. In a rat model with features of MetS (Dahl salt-sensitive rats fed with high-fat, high-salt diet) that were treated with vehicle, AZL-M (3 mg/kg per day), CLD (5 mg/kg per day) or AZL-M + CLD for 26 days, both AZL-M and CLD reduced blood pressure compared with vehicle, with further reduction when the two were combined. Additionally, nephrinuria was 57% lower and proteinuria was 47% lower with combination therapy compared with AZL-M alone [29].

As regarding the pharmacokinetic and pharmacodynamic characteristics of these two molecules, a model was developed to study spontaneously hypertensive rats after the oral administration of AZL-M and/or CLD. The drug concentration and pharmacological effects, including SBP and DBP were measured by liquid chromatography-tandem mass spectrometry and tail-cuff manometry, respective. The results revealed that the antihypertensive effect of AZL-M was significantly improved when combined with CLD, with a synergistic pharmacodynamic interaction [30].

CONCLUSION

In conclusion, a fixed dose combination therapy of azilsartan medoxomil and chlorthalidone appears to be an attractive option in the treatment of hypertension, with proven higher and longer lasting efficacy, as well as greater reduction of the risk of cardiovascular events in comparison to more traditional and widely used treatment options. This new combination, however, should be further studied in the future to obtain a more complete view of the benefits of this therapeutic combination in the treatment of hypertension.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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